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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Policy on Acute Inhalation Toxicity Data Waivers

FROM: Penelope A. Fenner-Crisp, Director
Health Effects Division (H7509C) 12/8/91

TO: Anne E. Lindsay, Director
Registration Division (H7505C)

This is in response to your memorandum of October 25, 1991 concerning the determination of a vapor pressure regulatory limit for the waiver of acute inhalation toxicity studies. HED has considered this issue and has concluded that low vapor pressure is not a key factor in determining whether an acute inhalation study for a pesticide formulation should be waived. Rather, the possibility of the generation of respirable particles or vapors is the more relevant criterion. Vapor pressure plays only a minor role in this determination.

The issues involved in the decision to waive an acute inhalation toxicity study are discussed in the attached interim policy paper. Because the issues are complex and dependent on the specific composition of each product, decisions on whether to waive these studies must be made on a case-by-case basis. The principles embodied in the examples described in the attached policy paper form the criteria on which these data waiver decisions should be based.

We have discussed this policy with Tom Ellwanger of your staff. He agrees in principle with the policy, but wants to discuss it further with the personnel that will be affected by it.

Please let me know if any additional clarification of this policy is needed.

Attachments

cc: R. Schmitt, HED
K. Baetcke, TOX I
R. Gardner, TOX I
J. Redden, TOX I
J. Whalan, TOX I
M. Van Gemert, TOX II
W. Burnam, SACB

INTERIM POLICY

WAIVER CRITERIA FOR INHALATION STUDIES

CFR §158.340, Note 16 states that for technicals and all formulations an acute inhalation study is, "Required if the product consists of, or under conditions of use will result in, an inhalable material (e.g. gas, volatile substances, or aerosol/particulate)." The three forms of inhalable materials can be more simply stated as gases, vapors, and aerosols. For clarity, a few definitions are offered:

A **gas** is a substance which normally occurs in the gaseous state at standard temperature and pressure (e.g. nitrogen, freon).

A **vapor** is a substance which normally exists as a liquid or solid at standard temperature and pressure that is dispersed in air in its gaseous state (e.g. methanol, iodine).

An **aerosol** is a suspension of solid particles (dusts, fumes, smoke) or liquid particles (mists, fogs) in a gas.

Vapor pressure is the pressure exerted by the gaseous state over the normal liquid and solid states. If a chemical's vapor pressure and molecular weight are known, the maximum obtainable vapor concentration in mg/l can be calculated as follows:

Maximum obtainable vapor concentration (ppm) =

$$\frac{\textit{Vapor Pressure (mm Hg)}}{760\ \textit{mm Hg (Atmospheric Pressure)}} \times (1 \times 10^6)$$

Concentration in mg/l =

$$\frac{\textit{Concentration (ppm)} \times \textit{Molecular Weight}}{24.5 \times 1000}$$

Aerodynamic particle size is a measure of particle size that takes into account the diameter and mass of a particle. The distribution of aerodynamic particle sizes is measured with a cascade impactor, and is reported in micrometers (μm) with a geometric standard deviation (σ_g). These data are used to estimate where the particles might be deposited along the respiratory tract. Although the term "particle size" is commonly used in inhalation studies, it always refers to aerodynamic particle size and bears no resemblance to optical or sieve particle sizing which measure only particle diameter. Aerodynamic particle sizing is often done for vapor studies because vapors tend to condense and form aerosols.

Inhalable materials include all gases and vapors, and aerosol particles fine enough to enter the nose and mouth. Although the current HED cutoff criterion for inhalability is 15 μm, much larger particles can be inhaled. Most large particles (approximately >8 μm in human, >2 μm in rodents) are captured in the nasal region, where soluble materials may be absorbed and insoluble materials are cleared. Smaller particles pass deeper into the respiratory tract.

Respirable materials are capable of entering the lung alveoli. While these particles can range up to 10μm, most large particles are deposited along the respiratory tract before reaching the lung. A respirable particle in man and rodent is defined as having an aerodynamic particle size of $\leq$1 μm.

Acute toxicity studies are important because most serious pesticide poisonings involve acute exposure. All reasonable efforts should be taken to perform acceptable acute inhalation studies in order to characterize the toxicity of the technical and demonstrate the potential inhalation hazards that could result from use of the formulation. Waivers should be granted sparingly and judiciously. Although it is preferable to have inhalation toxicity data for both the technical and the formulation, it may not be possible to do both.

Acute inhalation study waiver requests are occasionally submitted to the Toxicology Branches. These waivers can be granted provided the Registrant adequately demonstrates that inhalation exposure will not occur under conditions of use, and/or an inhalation study cannot reasonably be performed. Some pesticides are by their nature impossible to generate in inhalable form and thus pose no inhalation hazard. These include some waxes, resins, high viscosity liquids, micro-encapsulated products, and non-friable granules.

Low vapor pressure cannot be used exclusively to justify a waiver because there are too many other variables involved, including method of application, maximum attainable concentration, and overall toxicity of the substance. A chemical with a low vapor pressure may still be an inhalation hazard. Thus, it is impossible to designate a definitive cut-off vapor pressure to use in resolving waiver issues.

All petitions for waivers must be considered on a case-by-case basis. It is not possible to develop a policy to cover all contingencies. The following hypothetical waiver requests with discussions of their merits and options are provided as guidance in the decision process:

1. <u>The end-use product will be applied as a coarse spray or dust with particles too large to be inhaled</u>.

   Most acute inhalation study waivers are for products applied as dusts or sprays with large particle sizes. These waivers are usually denied because it is likely that some of the particles may be inhalable (capable of entering the upper respiratory tract), and possibly even respirable. The Registrants are urged to mill solids into fine powders, and to use nebulizers that yield the smallest particle size possible.

2. The technical has a low vapor pressure and is a high viscosity liquid, wax, or resin that cannot be generated as an aerosol.

Rather than granting a waiver in this case, the test substance for the study should be a solution of the technical. If the technical is water soluble, it should be mixed with water to lower its viscosity and facilitate nebulization. If it is non-polar, it could be mixed with a non-polar vehicle such as alcohol in order to reduce its viscosity, but this will introduce vehicle toxicity. Current EPA Guidelines do not require a vehicle control group unless the toxicity of the vehicle is unknown (this policy may change when the Guidelines are revised). If a study can be performed using the end-use product, a waiver should be granted for the unwieldy technical.

3. Because of a technical's low vapor pressure, insufficient vapor can be generated to induce toxicity.

The fact that a technical's low vapor pressure may preclude generating sufficient vapor does not rule out testing with an aerosol (the maximum obtainable vapor concentration can be calculated using the formulas listed under the definition for vapor pressure). Any chemical which cannot be generated as an aerosol and has a low vapor pressure is an excellent candidate for a waiver.

For example, if a formulation containing one or more low vapor pressure insecticides is sprayed onto baseboards, it should be tested because of the potential hazard of exposure to fine aerosol particles. If the same insecticide is applied as a waxy formulation, there may be no inhalation exposure during application.

4. A pesticide is used in a slow release collar or ear tag. Must the collar or tag be ground up for acute inhalation toxicity testing?

Plastic collars and ear tags are designed to provide slow-release dermal exposure to pesticides. Because there is minimal inhalation exposure, and because it is impractical to grind up collars and tags to produce inhalable particles, waivers should be granted in most cases. If the technical is expected to pose an inhalation hazard due to high volatility and toxicity (i.e.low LC_{50}), exposure testing will be required. Exposure to vapors is not applicable to toxicity data waivers.

5. A resinous pesticide is Category II by the oral route. Neither the technical nor the end-use product can be generated for inhalation toxicity testing. Waivers have been granted for both because there is no likelihood of exposure. When the pesticide is used, however, the end-use product is mixed with diesel fuel and sprayed from aircraft. This mixture is potentially inhalable.

An acute inhalation toxicity study of the end-use product should be performed using the diesel fuel solvent. A vehicle control group should be considered in the study

protocol. This is the only reasonable way to assess the toxicity of the pesticide by the inhalation route, and it tests the only use pattern that poses an inhalation hazard.

6. The end-use formulation is a non-friable granule.

As long as the granules remains intact, there is no need for an inhalation study of the formulation because the granules are not inhalable. The Registrant must demonstrate that the granules do not produce fine particles when subjected to shipping and handling. A simulation is required followed by particle sizing.

7. The end-use formulation is microencapsulated.

Some micro-encapsulated products are prime candidates for inhalation study waivers because they tend to be large (i.e. generally not inhalable), their shells are nontoxic plastic, and they are difficult or impossible to generate as inhalable particles. Nevertheless, each must be considered individually. Capsules that are readily fractured or dissolved, time-released, leaky, or small in size should be subject to inhalation studies, probably using homogenized or dissolved capsules.

Prepared by John E. Whalan
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